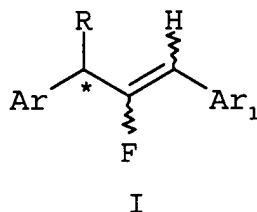


WHAT IS CLAIMED IS:

1. A process for the preparation of a chiral compound of formula I



wherein

Ar is phenyl optionally substituted with any combination of from one to three halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, C₁-C₄haloalkoxy or hydroxy groups,

1- or 2-naphthyl optionally substituted with any combination of from one to three halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups, or

a 5- or 6-membered heteroaromatic ring optionally substituted with any combination of from one to

three halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups;

R is C₁-C₄alkyl, C₁-C₄haloalkyl, C₃-C₆cycloalkyl or C₃-C₆halocycloalkyl;

Ar₁ is phenoxyphenyl optionally substituted with any combination of from one to six halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,

phenyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl,

C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,

biphenyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,

phenoxypyridyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,

benzylpyridyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,

benzylphenyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,

benzoylphenyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,

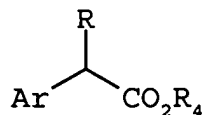
1- or 2-naphthyl optionally substituted with any combination of from one to three halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups, or

a 5- or 6-membered heteroaromatic ring optionally substituted with any combination of from one to three halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups, and

the (E)- and (Z)- isomers thereof,

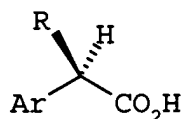
which process comprises the following steps:

a) treating a racemic ester of formula II



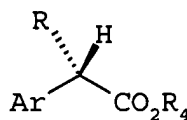
II

wherein Ar and R are defined as hereinabove and R₄ is C₁-C₄alkyl with an esterase to form a first mixture of either R-acid IIIa and S-ester IIIb



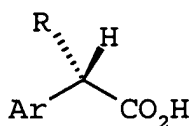
IIIa

and



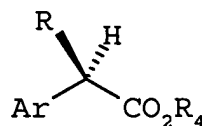
IIIb

or of S-acid IIIc and R-ester IIId



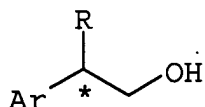
IIIc

and



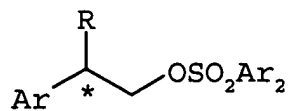
IIId

- b) separating said acid IIIa or IIIc from said ester IIIb or IIId;
- c) reducing said acid IIIa or IIIc or said ester IIIb or IIId to obtain a chiral alcohol IV having the R- or S-configuration



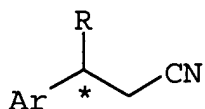
IV

- d) reacting said chiral alcohol with an arylsulfonyl halide Ar₂SO₂X wherein Ar₂ is phenyl, p-chlorophenyl, or p-tolyl, and X is chloro, bromo or fluoro to afford a sulfonate of formula V



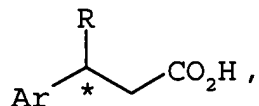
V

e) reacting said sulfonate V with a cyanide-delivering agent to afford a nitrile of formula VI



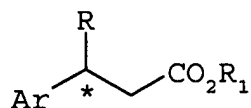
VI

f) hydrolyzing said nitrile VI to afford an acid of formula VII



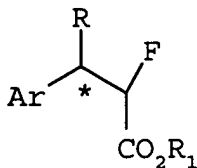
VII

g) esterifying said acid VII with an alcohol R_1OH , wherein R_1 is C_1 - C_4 alkyl to afford an ester of formula VIII



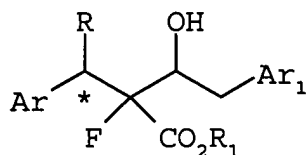
VIII

h) fluorinating said ester to afford a fluoro-ester of formula IX



IX

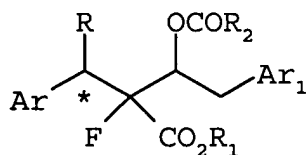
i) reacting said fluoro ester with an aldehyde $\text{Ar}_1\text{CH}_2\text{CHO}$, wherein Ar_1 is defined as hereinabove, in a solvent in the presence of a base to afford a second mixture of 4 chiral diastereomeric hydroxy-esters of formula X;



X,

j) optionally separating said second mixture X into a third mixture Xa and a forth mixture Xb, each mixture having two chiral diastereomers;

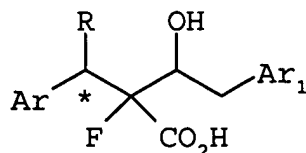
k) treating said hydroxy-ester mixture X, Xa or Xb with an acylating agent R_2COX_1 , wherein R_2 is C_1 - C_4 alkyl and X_1 is Cl, Br or R_2COO , to afford a fifth mixture of 4 chiral diastereomeric acyloxy esters XI, a sixth mixture of 2 acyloxy esters of formula XIa, or a seventh mixture of 2 chiral diastereomeric acyloxy esters XIb



XI,

l) optionally separating said sixth or seventh mixture into essentially pure chiral diastereomeric acyloxy esters;

m) hydrolyzing said pure chiral acyloxy esters or mixtures of esters of formula XI to afford a hydroxy-acid of formula XII,



XII

and

n) heating said hydroxy-acid XII with an arylsulfonyl halide $\text{Ar}_3\text{SO}_2\text{X}_2$, wherein Ar_3 is phenyl, p-chlorophenyl, or p-tolyl, and X_2 is chloro or bromo to afford the desired chiral compound of formula I.

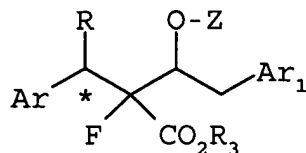
2. The process according to claim 1 wherein said esterase is horse liver esterase.

3. The process according to claim 1 wherein said base is lithium diisopropylamide.

4. The process according to claim 1 wherein said solvent is tetrahydrofuran.

5. The process according to claim 1 wherein R_4 is methyl.

6. A chiral compound of the following formula



XIII

wherein

Ar is phenyl optionally substituted with any combination of from one to three halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, C₁-C₄haloalkoxy or hydroxy groups,
1- or 2-naphthyl optionally substituted with any combination of from one to three halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups, or
a 5- or 6-membered heteroaromatic ring optionally substituted with any combination of from one to three halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups;

R is C₁-C₄alkyl, C₁-C₄haloalkyl, C₃-C₆cycloalkyl or C₃-C₆halocycloalkyl;

Ar₁ is phenoxyphenyl optionally substituted with any combination of from one to six halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,
phenyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,
biphenyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,
phenoxypyridyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,
benzylpyridyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,

benzylphenyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,

benzoylphenyl optionally substituted with any combination of from one to five halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups,

1- or 2-naphthyl optionally substituted with any combination of from one to three halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups, or

a 5- or 6-membered heteroaromatic ring optionally substituted with any combination of from one to three halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups, and

R₃ is H or C₁-C₄ alkyl; and

Z is H or COR₂, wherein R₂ is C₁-C₄ alkyl.

7. The compound according to claim 6 wherein Ar is phenyl optionally substituted with any combination of from one to three halogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy or C₁-C₄haloalkoxy groups; and R is C₁-C₄alkyl or C₃-C₆cycloalkyl.

8. The compound according to claim 7 wherein Ar₁ is phenyl optionally substituted with one to three halogen groups; and R is C₃-C₆cycloalkyl.

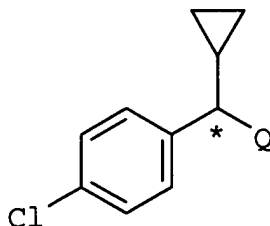
9. The compound according to claim 8 selected from the group consisting of

methyl (2S,3S)-2-[(R)-(4-chlorophenyl)(cyclopropyl)-
 methyl]-2-fluoro-4-(4-fluoro-3-phenoxyphenyl)-
 butanoate;
 methyl (2R,3R)-2-[(R)-(4-chlorophenyl)(cyclopropyl)-
 methyl]-2-fluoro-4-(4-fluoro-3-phenoxyphenyl)-
 butanoate;
 methyl (2S,3R)-2-[(R)-(4-chlorophenyl)(cyclopropyl)-
 methyl]-2-fluoro-4-(4-fluoro-3-phenoxyphenyl)-
 butanoate;
 methyl (2R,3S)-2-[(R)-(4-chlorophenyl)(cyclopropyl)-
 methyl]-2-fluoro-4-(4-fluoro-3-phenoxyphenyl)-
 butanoate;
 methyl (2S,3S)-2-[(S)-(4-chlorophenyl)(cyclopropyl)-
 methyl]-2-fluoro-4-(4-fluoro-3-phenoxyphenyl)-
 butanoate;
 methyl (2R,3R)-2-[(S)-(4-chlorophenyl)(cyclopropyl)-
 methyl]-2-fluoro-4-(4-fluoro-3-phenoxyphenyl)-
 butanoate;
 methyl (2S,3R)-2-[(S)-(4-chlorophenyl)(cyclopropyl)-
 methyl]-2-fluoro-4-(4-fluoro-3-phenoxyphenyl)-
 butanoate;
 methyl (2R,3S)-2-[(S)-(4-chlorophenyl)(cyclopropyl)-
 methyl]-2-fluoro-4-(4-fluoro-3-phenoxyphenyl)-
 butanoate;
 methyl (2S,3S)-3-(acetyloxy)-2-[(S)-(4-chlorophenyl)-
 (cyclopropyl)methyl]-2-fluoro-4-(4-fluoro-3-
 phenoxyphenyl)butanoate;
 methyl (2R,3R)-3-(acetyloxy)-2-[(S)-(4-chlorophenyl)-
 (cyclopropyl)methyl]-2-fluoro-4-(4-fluoro-3-
 phenoxyphenyl)butanoate;
 methyl (2R,3R)-3-(acetyloxy)-2-[(S)-(4-chlorophenyl)-
 (cyclopropyl)methyl]-2-fluoro-4-(4-fluoro-3-
 phenoxyphenyl)butanoate;

methyl (2S,3R) -3- (acetyloxy) -2- [(S) - (4-chlorophenyl) -
 (cyclopropyl) methyl] -2-fluoro-4- (4-fluoro-3-
 phenoxyphenyl) butanoate;
 methyl (2S,3S) -3- (acetyloxy) -2- [(R) - (4-chlorophenyl) -
 (cyclopropyl) methyl] -2-fluoro-4- (4-fluoro-3-
 phenoxyphenyl) butanoate;
 methyl (2R,3R) -3- (acetyloxy) -2- [(R) - (4-chlorophenyl) -
 (cyclopropyl) methyl] -2-fluoro-4- (4-fluoro-3-
 phenoxyphenyl) butanoate;
 methyl (2R,3S) -3- (acetyloxy) -2- [(R) - (4-chlorophenyl) -
 (cyclopropyl) methyl] -2-fluoro-4- (4-fluoro-3-
 phenoxyphenyl) butanoate;
 methyl (2S,3R) -3- (acetyloxy) -2- [(R) - (4-chlorophenyl) -
 (cyclopropyl) methyl] -2-fluoro-4- (4-fluoro-3-
 phenoxyphenyl) butanoate;
 (2S,3S) -2- [(S) - (4-chlorophenyl) (cyclopropyl) methyl] -2-
 fluoro-4- (4-fluoro-3-phenoxyphenyl) -3-hydroxy-
 butanoic acid;
 (2R,3R) -2- [(S) - (4-chlorophenyl) (cyclopropyl) methyl] -2-
 fluoro-4- (4-fluoro-3-phenoxyphenyl) -3-hydroxy-
 butanoic acid;
 (2R,3S) -2- [(S) - (4-chlorophenyl) (cyclopropyl) methyl] -2-
 fluoro-4- (4-fluoro-3-phenoxyphenyl) -3-hydroxy-
 butanoic acid;
 (2S,3R) -2- [(S) - (4-chlorophenyl) (cyclopropyl) methyl] -2-
 fluoro-4- (4-fluoro-3-phenoxyphenyl) -3-hydroxy-
 butanoic acid;
 (2S,3S) -2- [(R) - (4-chlorophenyl) (cyclopropyl) methyl] -2-
 fluoro-4- (4-fluoro-3-phenoxyphenyl) -3-hydroxy-
 butanoic acid;
 (2R,3R) -2- [(R) - (4-chlorophenyl) (cyclopropyl) methyl] -2-
 fluoro-4- (4-fluoro-3-phenoxyphenyl) -3-hydroxy-
 butanoic acid;

(2R,3S)-2-[(R)-(4-chlorophenyl)(cyclopropyl)methyl]-2-fluoro-4-(4-fluoro-3-phenoxyphenyl)-3-hydroxybutanoic acid; and
 (2S,3R)-2-[(R)-(4-chlorophenyl)(cyclopropyl)methyl]-2-fluoro-4-(4-fluoro-3-phenoxyphenyl)-3-hydroxybutanoic acid.

10. A chiral compound of the following formula



wherein

Q is $-\text{CO}_2\text{H}$; $-\text{CO}_2\text{CH}_3$; $-\text{CH}_2\text{OH}$; $-\text{CH}_2\text{OSO}_2\text{Ar}_2$; $-\text{CH}_2\text{CN}$; $-\text{CH}_2\text{CO}_2\text{H}$; $-\text{CH}_2\text{CO}_2\text{R}_1$; or $-\text{CHFCO}_2\text{R}_1$;

Ar_2 is phenyl, p-chlorophenyl or p-tolyl; and

R_1 is C_1 - C_4 alkyl.

11. The compound according to claim 10 selected from the group consisting of

(2R)-2-(4-chlorophenyl)-2-cyclopropylethyl 4-methylbenzenesulfonate;

(2S)-2-(4-chlorophenyl)-2-cyclopropylethyl 4-methylbenzenesulfonate;

(3R)-3-(4-chlorophenyl)-3-cyclopropylpropanenitrile;

(3S)-3-(4-chlorophenyl)-3-cyclopropylpropanenitrile;

(3R)-3-(4-chlorophenyl)-3-cyclopropylpropanoic acid;

(3S)-3-(4-chlorophenyl)-3-cyclopropylpropanoic acid;

methyl (3R)-3-(4-chlorophenyl)-3-cyclopropylpropanoate;

methyl (3S)-3-(4-chlorophenyl)-3-cyclopropylpropanoate;

[illegible]